EXHIBIT E

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SUCCESSFUL FIRST-TIME USE OF ANTIBODIES TO INTERFERON-γ ALONE AND COMBINED WITH ANTIBODIES TO TUMOR NECROSIS FACTOR-α TO TREAT RHEUMATIC DISEASES (RHEUMATOID ARTHRITIS, SYSTEMIC LUPUS ERYTHEMATOSUS, PSORIATIC ARTHRITIS, BEHÇET'S SYNDROME)

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***Summary:** A pilot study to test an anticytokine therapy consisting of antibodies to interferon-α (IFN-α), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), alone and in combination, was conducted with 25 patients with severe rheumatoid arthritis (RA) resistant to standard disease-modifying antirheumatoid drugs. Polyclonal IgG from this antibody was administered intramuscularly for 5 days to each of four groups of patients. Administration of the anticytokine antibodies led to rapid and evident clinical effect in the majority of patients. The study found an immediate (by day 7) therapeutic effect of antibodies to TNF-α and the combination therapy, and for the first time demonstrated the positive effect of anti-IFN-γ antibodies which was sustained to day 28. In addition to the clinical results obtained from patients with RA, anticytokine therapy was also tested in a small number of patients with psoriatic arthritis (PA), systemic lupus erythematosus (SLE), and Behçet's syndrome (BS) with very encouraging results. Further testing of this treatment must be done using repeated administrations of different kinds of antibodies alone or together with inmunodepressants. A theory explaining the role of the disturbance of cytokine production in the development of autoimmune diseases is expanded.*

Introduction

In 1974 we proposed that the development of autoimmune diseases (AD) was connected with the disturbance of the synthesis of interferons (IFN), and a therapeutic approach could be the neutralization of these cytokines (1). It was suggested that in AD, IFN is hyperproduced in the target cells and accumulates in the blood (2). Circulating interferon-α (IFN-α) was found in patients with various AD, while it was not detected in healthy subjects (2). This was confirmed in different laboratories (3,4). Later we proposed that most AD have the same underlying mechanism and that the disease varies depending on the cells affected (5). For example, in insulin-dependent

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diabetes mellitus (IDDM) IFN-α was detected on the surface of pancreatic islet cells (6), and in psoriasis, on specific cells within affected skin lesions (7). In systemic lupus erythematosus (SLE) psychosis IFN-α was found on certain brain cells (8). Later it was suggested that the hyperproduced IFN-α and possibly interferon-γ (IFN-γ) may be serum markers of AD (2,5).

The first anticytokine therapy was performed in 1977 (9). Anti-IFN-α (IgG) administered to 16 patients with very severe rheumatoid arthritis (RA) refractory to standard treatments led to significant improvement in clinical and laboratory parameters within 3-8 days after start of treatment. Joint swelling, joint constriction, pain, erythrocyte sedimentation rate (ESR), and other pathological signs and symptoms were significantly reduced. Four of the 16 patients regained mobility. The antibodies (IgG) to IFN-α, obtained after a prolonged immunization of donkeys with natural IFN-α, were given twice a day for 5 consecutive days. These data indicate the important role of cytokines in the development of AD. It became clear that cytokines, especially IFNs, are not neutral agents but can bring immune disease by prolonged circulation. After our publication clinical and experimental work confirmed this.

IFNs given to animal models of various AD in humans can exacerbate underlying autoimmune conditions (10-12). It was observed that the direct administration of IFN-α or IFN-γ triggered or exacerbated various ADs in different patients (13-16). On the other hand, antibodies to IFNs given to animal models of human AD halt or delay these diseases (17-19). The data confirmed our first clinical investigation, in which we gave antibodies to IFN-α to patients with good clinical effect. This is a rare case in which clinical data was confirmed later by experiment.

As is known, IFN-α participates in the induction of tumor necrosis factor-α (TNF-α) and its receptors (20), the most important element in inflammation. On the other hand, the formation of autoantigens in AD stimulates some T-cells to synthesize IFN-γ, which alone or in combination with TNF-α induces the production of HLA class II antigen, an important element in the pathogenesis of AD.

Thus in different AD one observes severe disturbance in the synthesis of cytokines, which brings about immunological chaos. We were the first to propose to remove IFN-α and IFN-γ (1, 5), which at that time was known as immune or lymphoid IFN (2, 9). From 1989-94 (21-26) we also proposed to remove TNF-α in combination with IFNs from patients with different AD. Recently, in 1993, chimeric monoclonal antibodies against TNF-α were reported to produce significant improvement in RA patients (27). One way in which anti-IFN-α therapy may exert its beneficial effect is through its inhibitory action on TNF-α, which appears to be the common pathway of inflammation.

As part of a large preliminary study to test our proposal that anticytokine therapy using multiple antibodies could be beneficial in treating AD, we administered antibodies to IFN-γ, IFN-α, and TNF-α separately and together to patients with active RA and certain other related AD. The latter was done in order to confirm our proposal that a single mechanism may underlie the development of different AD, but that the clinical manifestations differ depending on the cells affected by disturbed cytokine synthesis.

Materials and methods

Polyclonal antibodies were obtained by immunizing sheep with natural human IFN-α and goats with recombinant human (rHu) IFN-γ or rHu-TNF-α and isolating the IgG. Each milliliter of preparation contained 48-50 mg of protein. The antibodies had 80% specificity at 1:1,250 (anti-IFN-α) and 1:12,500 (anti-IFN-γ and anti-TNF-α) dilutions by ELISA (L. Tamarkin, CytoImmune Sciences, Inc., Columbia, MD).

A total of 30 patients were treated, 25 with active RA (20 tested in the first trial and 5 in another) and five with varied AD [two with psoriatic arthritis (PA), two with SLE, and one with Behçet's syndrome (BS)]. After obtaining ethical committee approval and informed consent of the patients, 20 patients with RA (16 were RF+), aged 27-64 (mean age 47), average disease duration 8 years, were equally randomized to one of four treatment groups. All patients met the criteria of the American College of Rheumatology for the diagnosis of RA and had not responded to at least four standard disease-modifying antirheumatoid drugs (DMARDs) (17 patients), could not tolerate them (two patients), or had refused to take them (one patient).

Other criteria for entry into the study included radiographic evidence of bone erosion, the presence of severe illness as indicated by the presence of six or more swollen joints and eight or more painful joints, plus at least two of the following criteria: >60 mins of continuous morning stiffness; fatigue >5 cm (visual analog scale); ESR >25 mm/hr; C-reactive protein >2 mg%; and absence of clinically significant concurrent diseases. Patients who were pregnant, had severe physical incapacity (Steinbrocker Class IV), a history of malignancy, or a history of serum sickness or other allergic reactions to foreign proteins, were excluded. DMARDs were withdrawn for at least 3 months prior to the trial but antiinflammatory therapy (NSAIDS and prednisolone up to 10 mg/day) was allowed if they were stable for at least 1 month before the trial. The same physician was used to make all assessments.

The first group received antibodies to IFN-α; the second, antibodies to IFN-γ; the third, antibodies to TNF-α; and the fourth, a combination of all three antibodies. All preparations were injected intramuscularly for 5 consecutive days. The patients were assessed daily for 7 days, then weekly up to the 28th day.

During the monotherapy, the daily dose of each antibody consisted of 96 mg on the first day and 144 mg on the next 4 days. During the combination therapy, each antibody was given at the daily dose of 96 mg. The additional five patients with RA were given a combination of IFN-γ and TNF-α antibodies.

Statistical significance ($p<0.05$) was determined using one-sample *t*-test on the difference in observations before and after treatment.

Results

A list of the clinical and laboratory measures used for the assessment of the efficacy and tolera-

Table 1 *Clinical and laboratory measures tested in patients with rheumatoid arthritis*

Pain, 0-10 cm (visual analog scale)
Morning stiffness, minutes
Number of swollen joints
Number of painful joints
Grip strength, kPa
Fatigue, 0-10 cm (visual analog scale)
C-reactive protein, mg%
Rheumatoid factor, latex-test (1:20=1)
Erythrocyte sedimentation rate, mm/hour
Hemoglobin
Leukocyte differential count
Thrombocytes
Transaminases
Bilirubin
Global assessment by physician*
Global assessment by patient*

* 5—Marked improvement
4—Improvement
3—Slight improvement
2—Unchanged
1—Deterioration

bility of the therapy is given in Table I. Nineteen of the 20 patients completed the 5-day course of injections. In the anti-IFN-α group, one patient who experienced fever and increase of joint pain after the first injection was withdrawn. In this group 7-day and 28-day results were assessed in four patients. In the combination group (receiving all three antibodies) one patient improved significantly after the first injections but exacerbation developed on the 8th day and prednisolone was given. Thus in this group 7-day results were assessed in five patients, and 28-day results in four patients.

Administration of the anticytokine antibodies across all groups led to rapid and evident clinical effect in the majority of patients. Improvement to some degree developed immediately after the first injection. Joint pain and the number of swollen joints decreased along with other measures. Fig. 1 presents graphs of indices showing the week-by-week mean response of all patients in each group from before treatment to the end of the 4th week. The graphs indicate the general course of the changes after the treatment was given in the indices shown. As can be seen, the most improvement across all groups occurred by day 7. The best effect by day 7 was achieved in patients treated with anti-TNF-α and the combination of the three antibodies (Table II). Nine and seven indices, respectively, showed statistically significant improvement in these groups. In the anti-IFN-γ group five indices improved significantly.

By day 28, the anti-IFN-γ group had sustained most of the improvement of day 7, while in the anti-TNF-α group, only two indices still showed signifi-

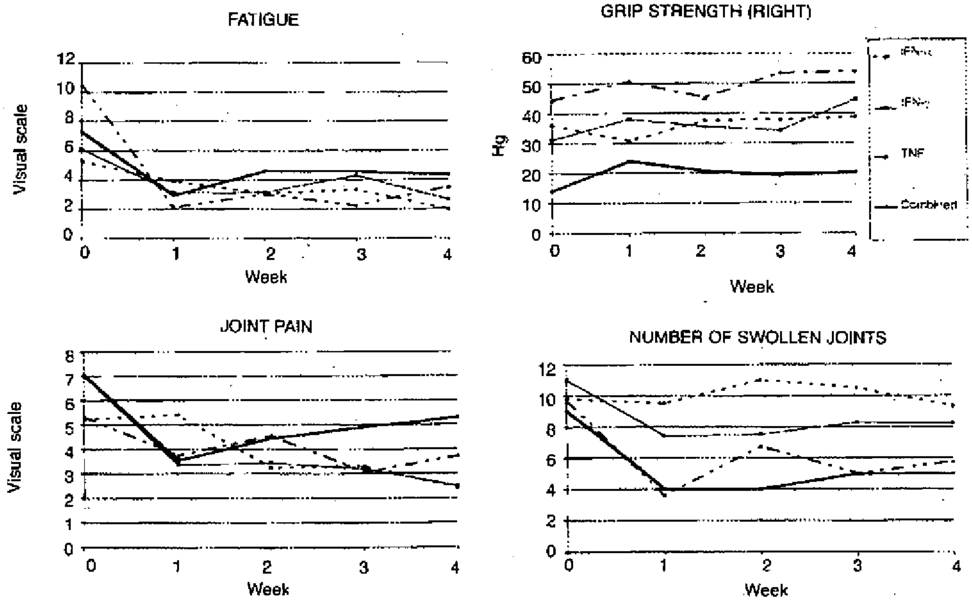

Fig. 1 Lines show week-to-week average improvement of each of the four treatment groups in rheumatoid arthritis.

Table II *Influence of anticytokine therapy on main clinical and laboratory indices (mean difference)*

	Day 7				Day 28			
	Anti-IFN-α	Anti-IFN-γ	Anti-TNF-α	Combination	Anti-IFN-α	Anti-IFN-γ	Anti-TNF-α	Combination
Pain, visual scale (0-10)	-1	-3.6*	-4.6*	-3.5*	-1.5	-5.1*	-1.9	-1.2
Morning stiffness (minutes)	-43	-76	-81*	-71*	-63	-53	-39	-60
Number of swollen joints	-1	-3.6*	-5.6*	-4.6*	+1	-2.8*	-3.2*	-3.8*
Number of painful joints	-4.8	-8.6*	-10.8*	-12.4*	-4.3	-10.4*	-8*	-10.3*
Grip strength (kPa): right	+5.3	+6.8	+12.4*	+10*	+0.8	+13.4*	+8	+7.3
left	+1.3	+9.4*	10.2*	+10	+0.5	9.4*	+5.6	+7
Fatigue, visual scale (0-10)	1.1	-3*	-4*	-4.3*	-2	-3.5*	-1.7	-2.4*
ESR mm/hr	+3	-4.2	-2.4	-1.2	+0.3	-5.8	-0.6	-1.7
C-reactive protein mg%	+2.1	+0.3	-2.5*	-1.8*	-0.1	+0.3	+0.1	-0.6
Rh factor, latex-test (1:20=1)	+1.3	+1	-1.2*	+0.5	0	+0.8	-0.6	0

Scores represent the mean difference observed in each treatment group between measures before treatment and at days 7 and 28. Statistical significance was determined by a one-sample *t*-test of the difference (*$p<0.05$). ESR = erythrocyte sedimentation rate.

cant positive changes, and in the combination group, three. Fig. 2 shows the comparative mean improvement (difference before and after treatment) among all treatment groups at day 7 and day 28 in six indices. A black arrow indicates which improvement is statistically significant (one-sample *t*-test, $p<0.05$).

After this trial was finished, an additional five patients were tested using a combination of two antibodies: anti-IFN-γ and anti-TNF-α. All patients had a positive response, confirming the results from the first trial using a combination of three antibodies.

The most frequent side effect of the therapy was a slight local itching (dermatitis) around the sites of injections. This seemed mostly attributable to the anti-IFN-α since most of the patients having this side effect had received this antibody (as monotherapy or in combination). This response developed on the 8th-10th days and disappeared spontaneously or after low doses of antihistamine drugs in 2-6 days. As we have already mentioned, one patient had a fever (38 °C) and increased joint pain after the first injection of anti-IFN-α. One patient on anti-IFN-α had very slight rhinopharyngitis on the 2nd day, and one patient in the anti-IFN-γ group had pulpitis on the 25th day. No changes in mean level of hemoglobin, leukocyte differential count, thrombocytes, transaminases, or bilirubin were observed.

In addition to these trials, a small number of patients with other AD were tested as a preliminary investigation of our theory that all AD have the same basis. So far two patients with SLE, two with PA, and one with BS have been tested. One

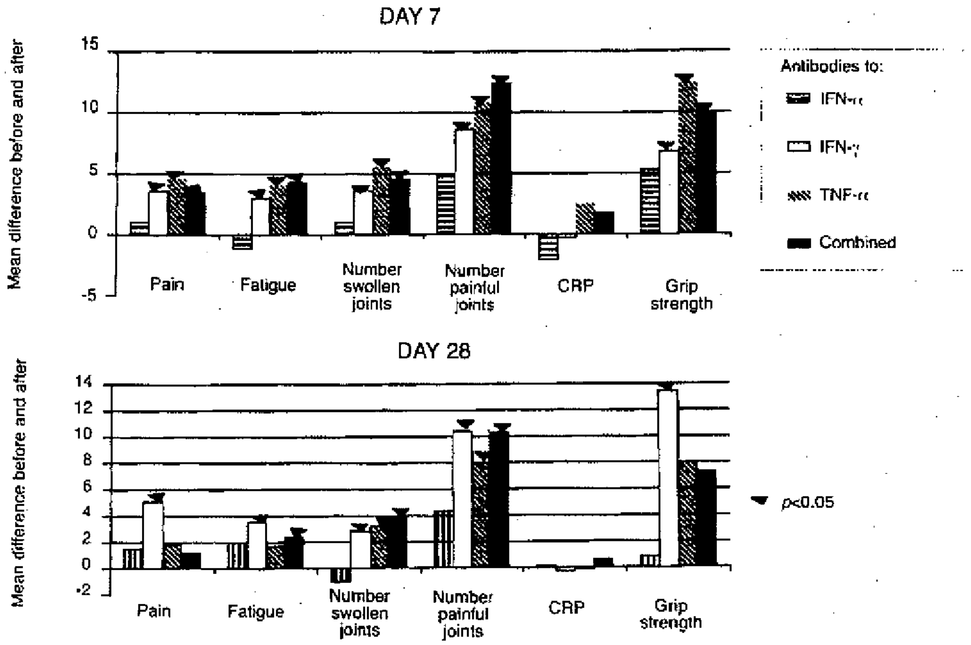

Fig. 2 Bars indicate the mean improvement in each of the 4 treatment groups betweeen day 0 and days 7 and 28 in 6 indices. Arrows indicate statistical significance of improvement (one-sample *t*-test). CRP = C-reactive protein

patient with SLE and two with PA received a combination of antibodies to IFN-γ and TNF-α using the same protocol as before. One patient with SLE received anti-IFN-γ alone and one patient with BS was given antibodies to IFN-α – the only one available at this time – also following the same protocol. All have shown either marked or moderate improvement after treatment according to their physician's global assessment (Table III). In all patients the pain in joints disappeared or decreased beginning the first week, as did skin lesions. In BS ulcers on the oral mucosa gradually disappeared, and laboratory parameters improved. One of the patients with SLE was withdrawn at day 8 due to an allergic reaction.

Discussion

Results of this study suggest the efficacy of anticytokine antibodies in patients who were for the most part completely resistant to conventional therapy. Thus, taking a general view of anticytokine therapy for AD, we can tentatively say that possibly three main cytokines – IFN-α, IFN-γ, and TNF-α – which induce other cytokines, are agents which can be manipulated for the purpose of regulating various autoimmune processes. Given our good previous results using anti-IFN-α, the poor results with anti-IFN-α here may be due to the very low titer of these antibodies compared with the earlier trial.

Table III *Anticytokine therapy in various rheumatic diseases*

	Day 7			Day 28		
	Psoriatic arthritis	SLE	Behçet's syndrome	Psoriatic arthritis	SLE	Behçet's syndrome
Marked improvement	1	2		1		1
Improvement	1		1	1	1	

Improvement in patients undergoing anticytokine therapy according to a global assessment of the data by the physician: anti-TNF-α and anti-IFN-γ antibodies in treatment of two patients with psoriatic arthritis and two patients with systemic lupus erythematosus (SLE). One SLE patient was withdrawn from the study due to an allergic reaction. Anti-IFN-α was used to treat one patient with Behçet's syndrome.

The data show that antibodies to TNF-α and the combination of antibodies exert an immediately apparent beneficial influence. What was interesting was that after 28 days, antibodies to IFN-γ maintained the improvement possibly better than did the anti-TNF-α antibodies. This suggests that the best results may be achieved through the use of these antibodies in some combination to achieve longer-term improvement.

Each of these cytokines (IFN-α, IFN-γ, TNF-α) may play its own pathological role and could be a single target in treatment. They are also involved in mutual induction and induction of other cytokines which carry on the pathological action. TNF-α mediates inflammation in AD as well as in certain other conditions; some subtypes of IFN-α and IFN-γ can trigger or exacerbate AD, while IFN-γ may intensify it. Thus we propose that IFN-γ, TNF-α and IFN-α may all play a very important role in the development of AD.

As was said previously, the development of AD may be connected with a single mechanism – the disturbance of cytokines themselves – but clinical manifestations may reflect the cell territory in which this mechanism takes place (5). Thus, we think that treatments of different AD can be very similar. In various AD different combinations of antibodies (three, two, or one) to these three cytokines could be used, sometimes possibly to other cytokines. For example, using only anti-IFN-α antibodies to treat BS showed good results. In the treatment of SLE and IDDM, in addition to antibodies to the main cytokines, we consider it reasonable to use antibodies to IL-6 also. Besides antibodies to cytokines, we also need to neutralize the pathological action of HLA class II antigens, which are induced by cytokines.

These preliminary data from the first use of anti-IFN-γ alone and combined with other anticytokines encourage further testing of the use of anti-IFN-γ and the combination anticytokine treatment in patients with other AD as well.

Various AD may require treatment with antibodies to different cytokines and antibodies to their receptors or combinations. Such therapy could be beneficial not only in different AD, but in certain allergies (bronchial asthma), AIDS, and in the prevention of rejection in transplantation (2,9,28,29). In the latter case antibodies to IFN II (IFN-γ), or in some cases antibodies to multiple types of IFNs or their receptors, should be used. Regarding AIDS, anti-IFN-α antibodies administered to patients with advanced AIDS – who typically have high titers of IFN-α in their blood – achieved beneficial results (26,30). Recently this was confirmed by removing IFN-α in AIDS patients, in this case by immunizing patients with an IFN-α vaccine (31). (The development of different methods to halt the production of cytokines and their receptors – chemical agents, genetic therapies, vaccines, *etc.* – could also be promising.)

In conclusion, anticytokine therapy could be a universal treatment for many different AD, including diseases of the nervous system (multiple sclerosis; MS) and psychiatric diseases *e.g.*, schizophrenia. In this connection, recently we obtained promising results in clinical trials in a joint Russian-American study of 22 patients with progressive MS using anti-IFN-γ antibodies, anti-TNF-α antibodies, and a combination of these two cytokine antibodies (32).

At the end of this article we would like to offer our ideas about the formation of autoantigens in AD. It is intriguing to contemplate that one of the reasons for the production of autoantigens may be a profound disturbance of IFN-α synthesis in cells in different AD with a genetic predeterminant or the influence of a specific agent (certain viruses, bacteria, or other components), and physical factors. A basic biochemical phenomenon in this situation is the loss or decrease of the repressor function in some subtypes of IFN-α (5, 24). This brings fundamental changes in the metabolism of the cells and the continuous production of IFN-α along with the formation of autoantigens or an autoantigenic complex which influences some T-lymphocytes and stimulates the production of IFN-γ. We propose that every autoantigen stimulates the production of a specific IFN-γ, which plays an important role in specific immunity and immunological memory. We think that IFN-γ, which is induced by specific autoantigens, is different from IFN-γ induced by mitogens or other IFN-γ inducers. The injection of normal IFN-α or -γ into the organism with an autoimmune condition and a disturbed synthesis of IFN-α or -γ will increase the function of the existing abnormal IFNs. At the same time, on the surface of cells where autoantigens are formed, the receptors to IFN-γ and TNF-α and possibly to other cytokines, and to HLA class I, II, and III antigens, are synthesized.

For the successful treatment of different AD and autoimmune conditions we need to use antibodies to certain cytokines and to their receptors which could be repeatedly administered over a long period of time. For this it is necessary to use humanized or chimeric monoclonal antibodies, Fab fragments, or purified polyclonal antibodies from one or more species. These can be administered along with immunodepressants.

Some autoimmune diseases and conditions connected with cytokine disturbance which could be treated by anticytokine therapy. Rheumatoid arthritis; systemic lupus erythematosus; amyotrophic lateral sclerosis; multiple sclerosis; myasthenia gravis; Sjögren's syndrome; rheumatism; scleroderma; vasculitis; bronchial asthma; idiopathic thrombocytopenic purpura; insulin-dependent diabetes mellitus; Crohn's disease; Graves' disease; Behçet's syndrome; pemphigus; Parkinson's disease; autoimmune diseases of the eye and ear; chronic fatigue syndrome; psoriasis; eczema; sarcoidosis; congenital AD; AIDS; genetic defects of immunity including congenital deficiency status (especially with the disturbance of intellect); Down's syndrome; chondrodystrophy; some cancers and leukemia; some psychiatric diseases with an autoimmune genesis such as schizophrenia and depression; autism; congenital deformities; leprosy; epilepsy; Alzheimer's disease; Ménière's disease; and the treatment of rejection in transplantation.

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